REMARKS

I. Preliminary Remarks

The Examiner objected to claims 21-29 for depending from a non-elected claim. In the foregoing amendment, claims 21-29 were amended to correct the dependencies. In addition, the Examiner objected to claims 6 and 7 for being improper multiple dependent claims. Claims 6 and 7 have been amended and dependent claims 31-38 were added to correct improper multiple dependencies. These amendments do not add new matter to the specification.

Claims 15-17 and 20 were canceled without prejudice because these claims were directed to a non-elected invention and not for any reason relating to patentability.

II. The Rejection under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn.

Claim 9 was rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Examiner asserted that the term "derived from" simian Ad SV-20 is indefinite. Applicants respectfully traverse.

Recombinant adenovirus vectors are constructed by modifying the genomes of naturally occurring adenoviruses. Thus, the term "derived from," as recited in claim 9, indicates that the recombinant adenovirus vectors were constructed using a simian adenovirus AV-99. Methods to modify a naturally occurring adenovirus in order to construct efficient, functional adenovirus vectors are well known in the art (See, *e.g.*, Graham and Prevac, *Molecular Biotechnology*, 3: 207-220, 1995; attached as **Exhibit A**). Therefore, claim 9 is not indefinite and Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

III. The Rejection under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The Examiner rejected claims 9, 14 and 19 under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The Examiner asserted that the claims are directed to novel biological materials (adenovirus strain deposited as

ATCC No. VR-199), and these materials must be readily available to the public. However, ATCC No. VR-199 is commercially available Simian adenovirus 20, strain M-12, as indicated in the ATCC product description attached as **Exhibit B**. This adenovirus strain was not deposited by the Applicants and is currently readily available to the general public. Therefore, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

IV. The Rejection under 35 U.S.C. § 102(b) Should Be Withdrawn.

Claims 1-3, 10-13, 21, 23, 24 and 30 were rejected under 35 U.S.C. § 102(b) as being anticipated by Natsoulis *et al.* (U.S. Patent No. 6,027,931). The Examiner stated that Natsoulis *et al.* teaches a cell transfected with an AAV vector and adenovirus, pRCM.globinpolyA, which expresses Rep78/68 at "about that of wild-type/p5 expression."

None of the vectors taught in Natsoulis *et al.* express Rep78/68 at about the level when expressed under the control of the AAV p5 promoter in its native conformation and overexpress Rep52/40 as recited in the pending claims. Natsoulis *et al.* provides the following vectors: pAAVAd, pRCM, pW1909, pRCM.kozak, pRCM.polyA, and pRCM.globinpolyA. The results described in Natsoulis *et al.* at column 15, lines 44-63 and Figure 2 are compared to the pending claims in the table below.

Nasoulis *et al.* Vector	Rep 78/68 expression level as under the control of the p5 promoter	Rep50/42 over expression
pAAVAd	Yes	No
pRCM	Yes	No
pW1909	No (decreased)	Yes (increased)
pRCM.kozak	Yes	No
pRCM.polyA	Yes	No
pRCM.globinpolyA	No (decreased)	Yes (increased)

Vectors pAAVAd and pRCM express Rep78/68 and Rep50/42 at the same level. Therefore, vector pRCM expresses Rep78/68 at about the level when expressed under the control of the AAV p5 promoter in its native conformation but does not overexpress Rep52/40 as recited in the pending claims. Vector pW1909 expressed very low levels of Rep78/68 and does not express Rep78/68 at about the level when expressed under the control of the AAV p5 promoter in its native conformation as recited in the pending claims. Vectors

pRCM.kozak and pRCM.polyA expressed Rep78/68 and Rep52/40 at about the level when expressed under the control of the AAV p5 promoter in its native conformation as the alterations in this vector has "no effect on Rep protein expression." Therefore, vectors pRCM.kozak and pRCM.polyA do not overexpress Rep52/40 as recited in the pending claims. Vector pRCM.globinpolyA decreased expression of Rep78/68 less than wild-type and increased expression of Rep52/40. Therefore, vector pRCM.globinpolyA does not express Rep78/68 at about the level expressed when under the control of the AAV p5 promoter in its native conformation as recited in the claims. (See Column 15, lines 44-63 of Natsoulis *et al.*). Therefore, the vectors taught in Natsoulis *et al.* do not literally or inherently anticipate or render obvious the pending claims.

Claims 1-3 of Natsoulis *et al.* are directed to vectors that produce greater quantities of the Rep50/42 proteins than the quantities of the Rep78/68 proteins, but the specification only teaches vectors that express decreased levels of the Rep78/68 proteins. In view of the specification of Natsoulis *et al.* the only interpretation of the disclosure and claims of Natsoulis *et al.* is the long form Rep proteins (Rep78/68) are down regulated and therefore, the claims of Natsoulis *et al.* cannot anticipate or render obvious the pending claims. For example, the Natsoulis *et al.* specification states the "AAV helper functions systems, host cells and methods of the present invention allow for high-efficiency production of rAAV virions by reducing the amount of long forms of Rep proteins produced. Here we [Natsoulis *et al.*] show that AAV helper function vectors that produce only small amounts of the long forms of the Rep proteins provide for higher titer virion productions." (See column 16, lines 52-57). Thus, the Natsoulis *et al.* specification indicates that the vectors express Rep78/68 at levels lower than that produced under the control of the p5 promoter in its native conformation. Therefore, Natsoulis *et al.* does not anticipate or render obvious the claims pending claims and the rejection should be withdrawn.

Claims 1-2, 10-13, 21, 23, 24 and 30 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Xiao *et al.* (*J. Virol.* 72(3): 2224-2232, 1998). The Examiner stated that Xiao *et al.* discloses transfection of 293 cells with a rAAV genome and re-cap proteins from several vectors. In particular, the Examiner stated that in the vectors of Xiao *et al.* "Rep78/68 expression was attenuated (considered, absent a precise definition, to be "about" wild-type level of expression) and Rep52/40 expression increased upon introduction

of an extra copy of the p5 promoter." However, the attenuated expression of Rep78 and Rep68 in the vectors taught in Xiao *et al.* was due to a mutation in the Rep78/68 start codon and therefore the level of Rep78 and Rep68 expression must be less than that expressed at under the control of the AAV p5 promoter in its native conformation, and the term "attenuated expression" refers to reduced expression, rather than normal expression under the AAV p5 promoter. Thus, the 293 cells containing helper AAV vectors, as taught in Xiao *et al.*, do not expressly or inherently anticipate the claimed helper vectors.

V. The Rejection under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 22, 26, 28 and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* (U.S. Patent No. 6,027,931) in view of Hardy (U.S. Patent No. 6,429,001). The Examiner stated that Hardy teaches that AAV host cells include the claimed cell types: HeLa, WI-38, MRC-5 and Vero. Similarly, claim 25 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Murphy (U.S. Patent No. 6,635,476). The Examiner stated that Murphy teaches that the PERC.6 cell line is useful for producing adenovirus and rAAV. Claims 27-29 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Potash *et al.* (U.S. Patent No. 5,911,998). The Examiner stated that Potash *et al.* teaches that the MRC-5, WI-38 and FRhL-2 cell lines may be used for vaccine production.

As stated above, Natsoulis *et al.* does not teach the claimed vectors that overexpress Rep52/40 and express Rep78/68 at about the level when under the control of the AAV p5 promoter in its native conformation. Further, the Natsoulis specification teaches that the high-efficiency production of rAAV virions is dependent upon reducing the level of Rep78/68 produced (See column 16, lines 52-55). Therefore, the references cited by the Examiner do not render the claims obvious and the rejection under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants believe pending claims 1-3, 5-10, 12-14, 18, 19 and 21-38 are in condition for allowance and early notice thereof is requested. If further discussion would expedite allowance of the claims, the undersigned can be contacted at the telephone number below.

Respectfully submitted,

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By _____
Sharon M. Sintich
Registration No.: 48,484
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant